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# Empirical and *ab initio* Calculations of Thermochemical Parameters of Amino Acids: IV.[1] Non-Typical Amino Acids: Hydroxyamino Acids, Thioamino Acids, and Heterocyclic Amino(imino) Acids

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**Abstract**—Using a set of computational methods we calculated the basic thermochemical characteristics of the fifteen non-typical L-α-amino acids of hydroxyaminocarboxylic and thioaminomonocarboxylic series, and of some heterocyclic amino(imino)carboxylic acids.

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The compounds considered in this study are mainly the derivatives of typical amino acids. They exhibit pronounced biological activity [2, 3]. For example, the typical amino acid cysteine is normally present in proteins in two forms: either cysteine itself, or as a non-typical amino acid cystine (**X**, see the table), whose molecule consists of two cysteine molecules linked covalently through a disulfide bridge formed at the oxidation of both thiol groups of two molecules of the amino acid [3]. Cystine **X** plays an important role in the formation of the insulin hormone and a variety of immunoglobulins (antibodies) [3]. Another amino acid, cystathionine **IX**, is formed in the body from the typical amino acid serine and homocysteine **IV,** and also exhibits a wide spectrum of biological activity [3].

Meanwhile, the thermochemistry of these amino acids is practically unknown. Thus, there are no published experimental data on enthalpies of sublimation and enthalpies of formation in the gas phase for all the compounds listed in the table. As for the formation enthalpy in the crystalline state, we found the experimental value for only one amino acid considered here, namely, the $\Delta H^0_{form}$ of cystine **X** [4].

We performed calculation by the additive scheme of the formation enthalpies of amino acids in the crystalline state and in the gas phase using the Enthalpy software [5] on the basis of published [6–8] and calculated by us earlier [9, 10] group contributions. The results of these calculations are shown in the table. Enthalpy of sublimation of amino acids were calculated similar to [1, 9, 10] from the difference in the formation enthalpies of compounds in the gas phase and in the crystalline state.

Unfortunately, the lack of sufficient experimental data made it impossible at this stage to perform an empirical calculation of the formation enthalpies in the crystalline state of penicillamine (**V**), djenkolic acid (**VII**), 1-methylhistidin (**XIII**), 2-methylhistidin (**XIV**) and 5-hydroxytryptophan (**XV**). For the same reason also it was impossible to calculate the enthalpies of sublimation of these amino acids.

Next, we performed the *ab initio* calculations of gas-phase formation enthalpies of amino acids. Based on the results of previous studies [1, 9], the B3LYP/6-31G(d) method again was chosen as a first approximation to find rapidly the optimal molecular conformations of the compounds. Then for the most energetically favorable conformations of amino acids we performed the calculation of their $\Delta H^0_{form}$ values by the B3PW91/cc-pVQZ method. The table shows the results of these calculations.

[1] For communication III, see [1].

Calculated and experimental formation and sublimation enthalpies of non-typical L-α-amino acids, kJ mol$^{-1}$

| Comp. no. | Compound | Formula | $\Delta H^0_{subl}$ (calculated) | $\Delta H^0_{form}$ (calculated) | | | |
|---|---|---|---|---|---|---|---|
| | | | | crystalline state, additive scheme | gas phase | | |
| | | | | | additive scheme | B3LYP/6-31G(d) | B3PW91/cc-pVQZ |
| | | | Hydroxyamino acids | | | | |
| **I** | Homoserine | $C_4H_9O_3N$ | 182.4 | –770.9 | –588.5 | –510.1 | –589.1 |
| **II** | Pantonine | $C_6H_{13}O_3N$ | 189.8 | –839.9 | –650.1 | –533.3 | –618.1 |
| **III** | Methyl tyrosinate | $C_{10}H_{13}O_3N$ | 176.3 | –636.4 | –460.1 | –345.1 | –477.6 |
| | | | Thioamino acids | | | | |
| **IV** | Homocysteine | $C_4H_9O_2SN$ | 169.3 | –568.1 | –398.8 | –302.6 | –387.4 |
| **V** | Penicillamine | $C_5H_{11}O_2SN$ | – | – | –437.9 | –317.9 | –406.4 |
| **VI** | S-Methylcistein | $C_4H_9O_2SN$ | 172.7 | –564.1 | –391.4 | –299.8 | –381.0 |
| **VII** | Djenkolic acid | $C_7H_{14}O_4S_2N_2$ | – | – | –728.4 | –571.5 | –721.2 |
| **VIII** | Lanthionine | $C_6H_{12}O_4SN_2$ | 303.6 | –1050.2 | –746.6 | –586.8 | –726.6 |
| **IX** | Cystathionine | $C_7H_{14}O_4SN_2$ | 312.2 | –1079.6 | –767.4 | –604.9 | –749.8 |
| **X** | Cystine | $C_6H_{12}O_4S_2N_2$ | 313.6 | –1051.3[a] | –737.7 | –569.9 | –724.9 |
| | | | Heterocyclic amines (amino acid) | | | | |
| **XI** | 4-Methylproline | $C_6H_{11}O_2N$ | 141.1 | –543.9 | –402.8 | –324.7 | –405.8 |
| **XII** | 4-Hydroxyproline | $C_5H_9O_3N$ | 172.5 | –712.9 | –540.4 | –444.0 | –538.3 |
| **XIII** | 1-Methylhistidin | $C_7H_{11}O_2N_3$ | – | – | –227.3 | –176.9 | –289.4 |
| **XIV** | 2-Methylhistidin | $C_7H_{11}O_2N_3$ | – | – | –298.2 | –218.7 | –342.1 |
| **XV** | 5-Hydroxytryptophan | $C_{11}H_{12}O_3N_2$ | – | – | –394.9 | –243.4 | –442.7 |

[a] Experimental value –1105.0 kJ mol$^{-1}$ [4].

Thus, the approach used in this study can be used further to obtain reliable calculation data of the thermochemical parameters of amino acids for which the corresponding experimental data do not exist.

All quantum-chemical calculations were carried out with the Gaussian 98 software [11] in the Interdepartmental Supercomputer Center of Russian Academy of Sciences (Kazan Branch) [11].

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